

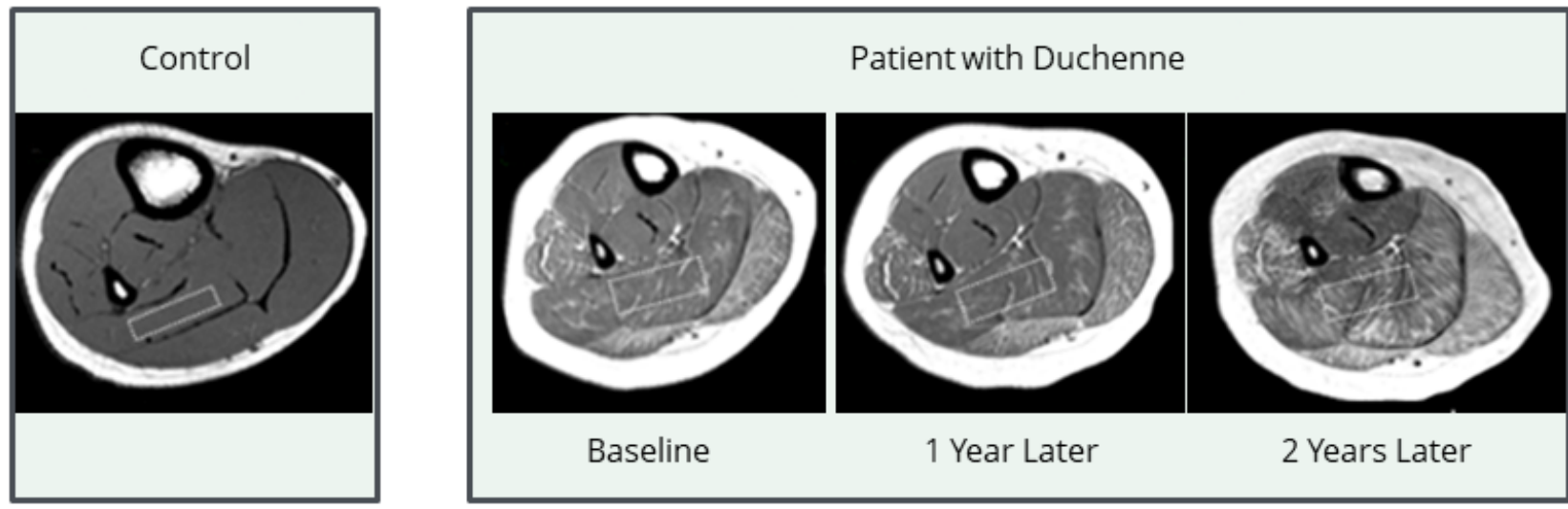
A Composite of MRI T2 of Five Lower Leg Muscles Is Highly Correlated with Timed Function Tests and Functional Status, and Supports Positive Effects of Edasalonexent in 4 to 7-Year Old Patients with Duchenne Muscular Dystrophy

Krista Vandenberg PT PhD¹, H. Lee Sweeney PhD¹, Richard S. Finkel MD², Rebecca J. Willcocks PhD¹, Erika L. Finanger MD⁴, Gihan I. Tennekoon MD³, Perry Shieh, MD PhD⁵, Glenn Walter PhD¹, William Rooney PhD⁴, Sean C Forbes PhD¹, William T. Triplett BSc¹, Alison Barnard, PhD¹, DJ Wang PhD³, Sabrina W. Yum MD³, Maria Mancini MHP⁶, James MacDougall PhD⁶, Angelika Fretzen PhD⁶, Joanne M. Donovan MD PhD⁶

¹ University of Florida Health, Gainesville, FL; ² Nemours Children's Health System, Orlando, FL; ³ The Children's Hospital of Philadelphia, Philadelphia, PA; ⁴ Oregon Health Sciences University, Portland, OR; ⁵ University of California, Los Angeles, Los Angeles, CA; ⁶ Catabasis Pharmaceuticals, Cambridge, MA

MRI is a Non-Invasive Approach to Assess Disease Progression in Duchenne

The ability of MRI parameters to assess disease progression in an objective and non-effort dependent way makes them attractive surrogate endpoints for clinical trials in DMD



MRI T2 and MRS fat fraction:

- Elevated in young boys with DMD and increase with age
- Changes correlate with speed of functional measures
- Changes correlate with loss of functional milestones
- Responsive to therapeutic intervention
- Predicts future loss of function

Willcocks et al. 2016, Ann. Neurol.; Willcocks et al. 2014, Ann. Neurol.; Barnard et al. 2018

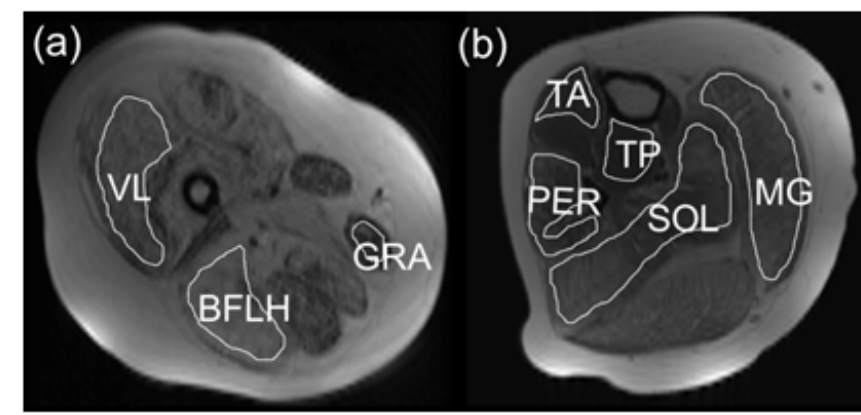
ImagingDMD: Largest Natural History Database of MRI in DMD

The ImagingDMD study performed systematic measurements of function and MRI annually in over 150 boys with DMD

- MRI T2 of 5 lower leg muscles and 3 upper leg muscles
- MRS T2 and fat fraction of soleus and vastus lateralis

The ImagingDMD study provides natural history data with the intent of validating MRI as biomarker for clinical trials

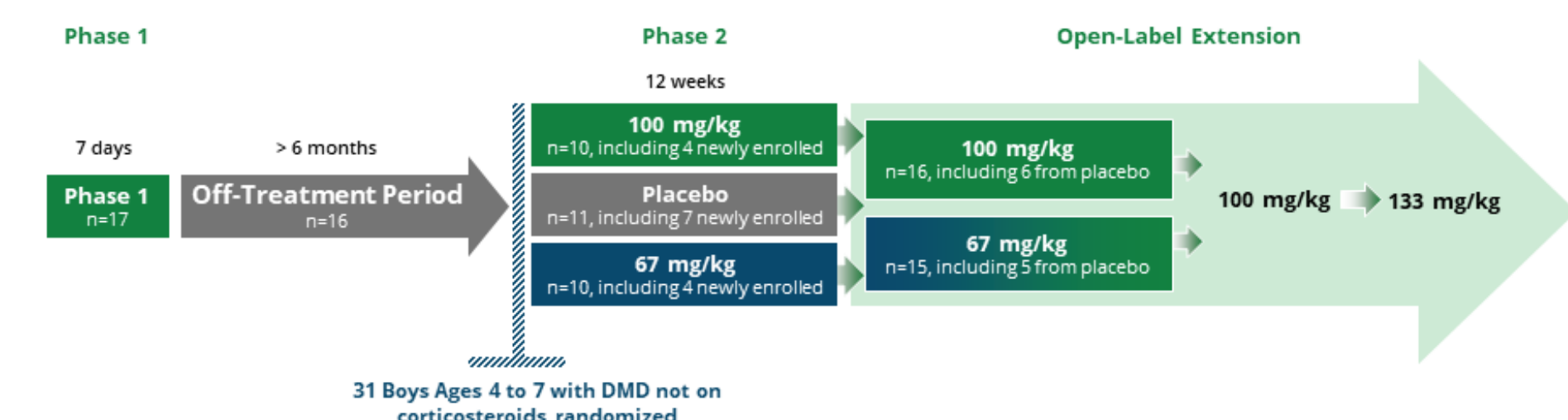
In MoveDMD study of edasalonexent, a MRI T2 composite of 5 lower leg muscles was used as primary endpoint



Rationale for composite of five lower leg muscles T2:

- Improve signal to noise
- Capture multiple muscles at potentially different stages of disease progression

MoveDMD Trial Incorporated MRI and Functional Measures



Integrated multi-part trial design

- Supports evaluation of efficacy, safety/tolerability, target engagement, and dose response

Off-treatment control period measurements between Phase 1 and commencement of dosing in Phase 2/open-label extension

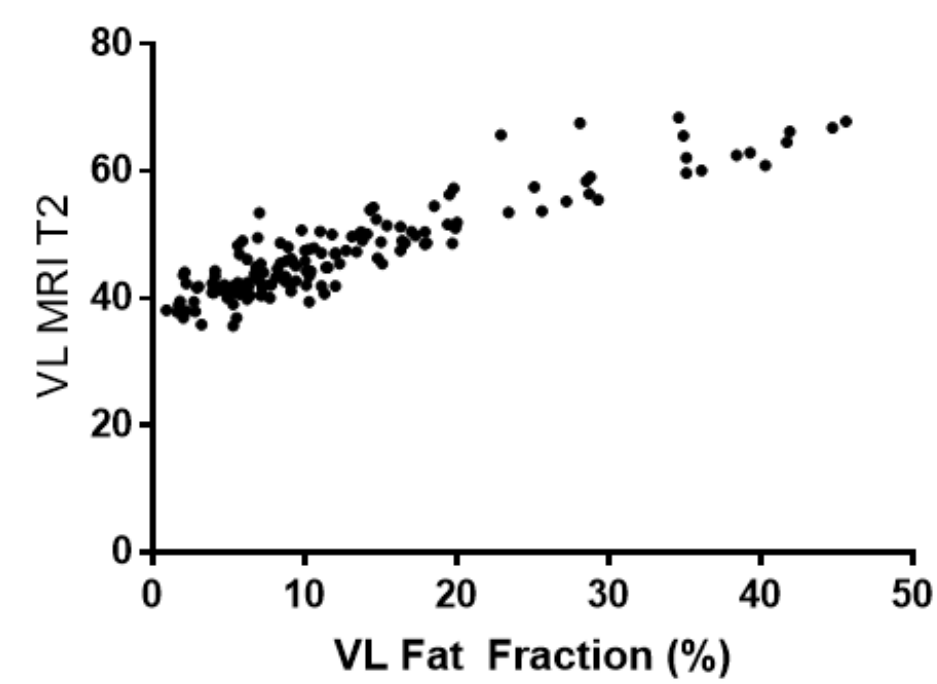
- Provides internal control for pre-specified MoveDMD analyses
- To confirm consistency of patient off-treatment control period disease progression with available natural history data

Open-label extension

- Planned comparison MRI measures to ImagingDMD natural history database

In Boys with DMD, MRI T2 is Largely Driven by Fat Fraction

Relationship of MRI T2 and MRS fat fraction of vastus lateralis



$p < 0.0001$
Spearman $r = 0.85$
Data from MoveDMD

MRI T2 detects inflammation and edema, muscle damage, and fat content

- Patients with DMD demonstrate increased T2 in leg muscles
- Increased T2 levels are evident in young boys with minimal fat fraction, suggesting T2 is an early indicator of pending fibrosis and fat replacement

MRI T2 is heavily influenced by deterioration of muscle and resultant fat infiltration

(Arpan, 2014; Willcocks, 2014 and 2016).

Lower Leg Composite is Tightly Correlated with Current Function as Assessed by TFTs and 6-Minute Walk Distance

Spearman Correlation Coefficient for MRI and Functional Measures

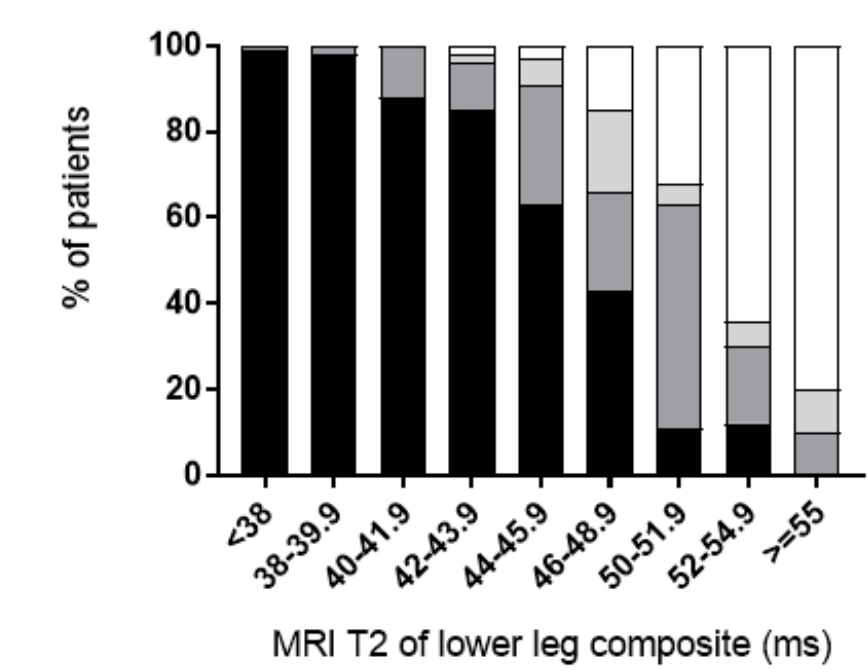
	Lower Leg Composite MRI T2	Soleus Fat Fraction*	Vastus Lateralis Fat Fraction*
4-Stair Climb Time	0.79	0.65	0.78
Time to Stand Time	0.79	0.60	0.77
10-meter Walk/Run Time	0.77	0.66	0.78
6 Minute Walk Distance	-0.65	-0.58	-0.68

*Data from Barnard, 2018

In the ImagingDMD database, the lower leg composite MRI T2 was highly correlated with timed function tests (TFTs) and 6-minute-walk distance, with correlations similar to previously reported values for the vastus lateralis and soleus FF

The lower leg composite MRI T2 was also highly correlated with the VL fat fraction ($r = 0.74$) and the soleus fat fraction ($r = 0.84$)

Loss of Functional Milestones Correlates with Lower Leg Composite MRI T2



Can perform TFTs as follows:

- none (non-ambulatory)
- only 10-meter walk / run
- 10-meter walk / run and 4-stair
- all TFT's, including stand from supine

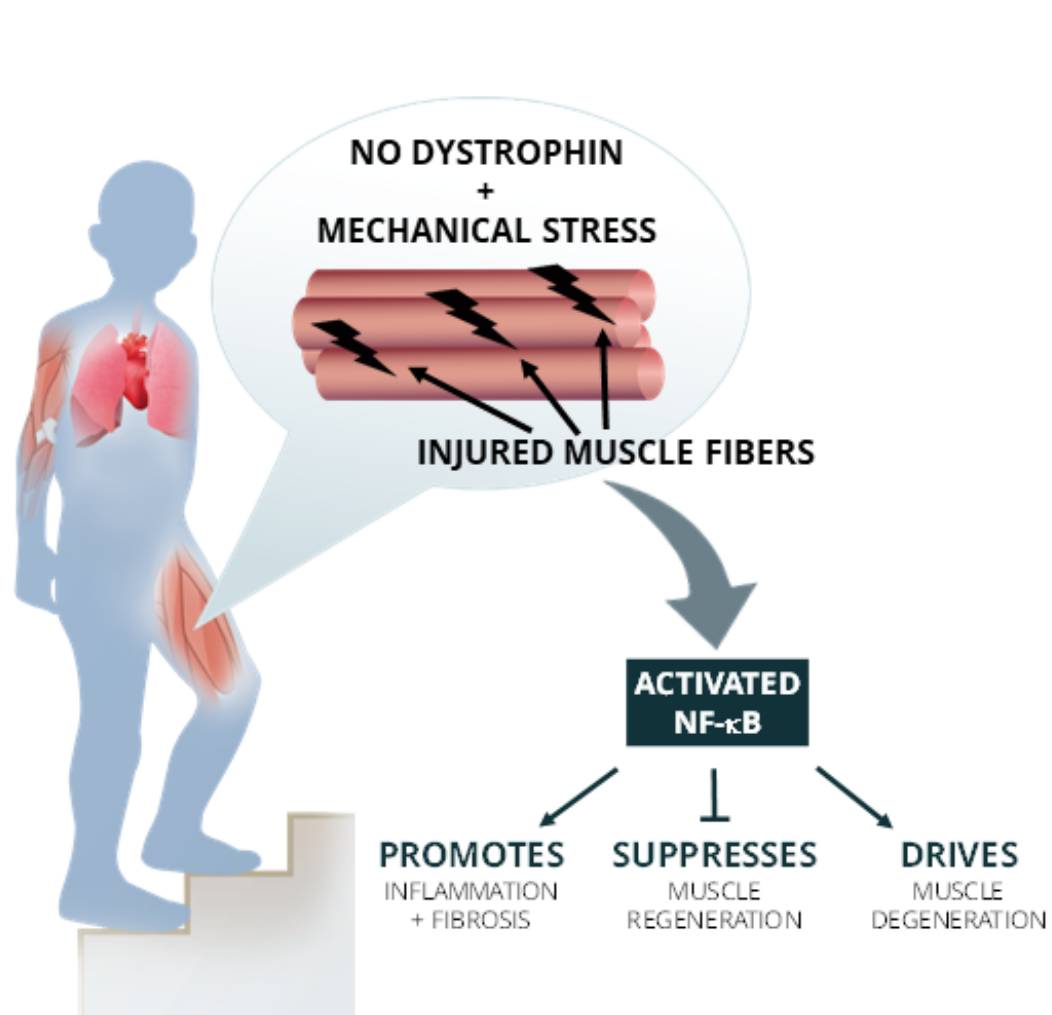
Barnard et al (2018) previously showed that loss of functional milestones was linked to vastus lateralis fat fraction. At VL fat fraction values up to 19%, 99% of the patients could perform all 3 timed function tests, but at fat fractions over 60%, over 50% were non-ambulatory

In the ImagingDMD natural history database, lower leg composite MRI T2 values also were highly correlated with loss of functional milestones

An ~2 ms increase in MRI T2 was associated with an appreciable change in the ability to perform all timed function tests.

MoveDMD Study : Edasalonexent

Edasalonexent Inhibits NF-κB, a Fundamental Driver of Disease Progression in DMD

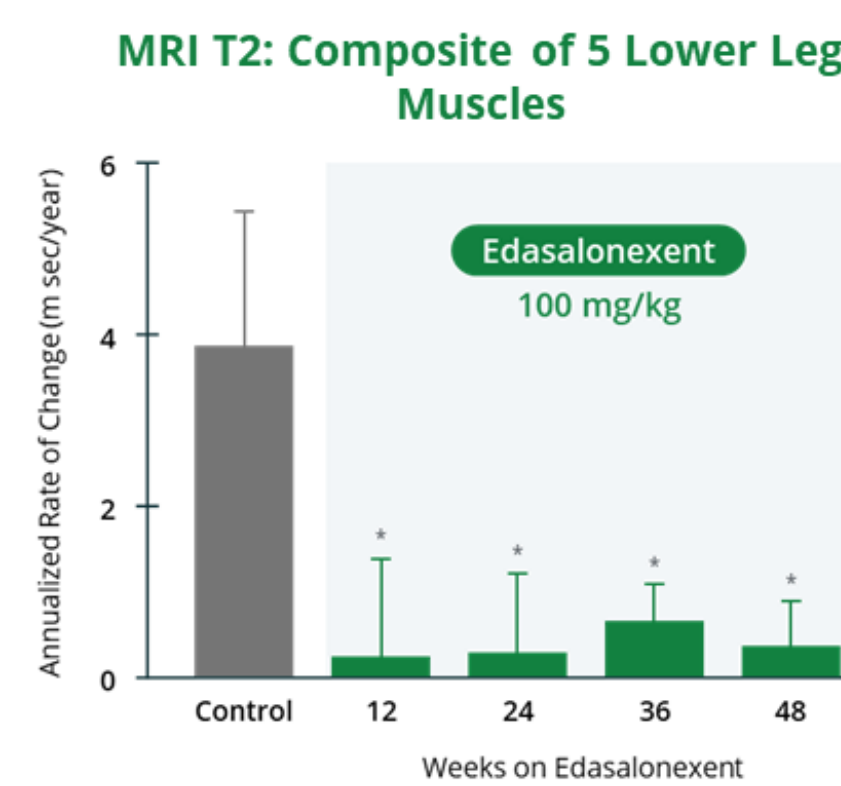


- Lack of dystrophin combined with mechanical stress activates NF-κB
- Edasalonexent inhibits NF-κB, which is the key link between loss of dystrophin and disease pathology and plays a fundamental role in the initiation and progression of skeletal and cardiac muscle disease in DMD

Kumar, et al. FASEB 2003 17(13):17:386-96.
Peterson, et al. Curr Top Dev Biol. 2011; 96: 85-119.
Hammers, et al. JCI Insight. 2016;1:e90341.

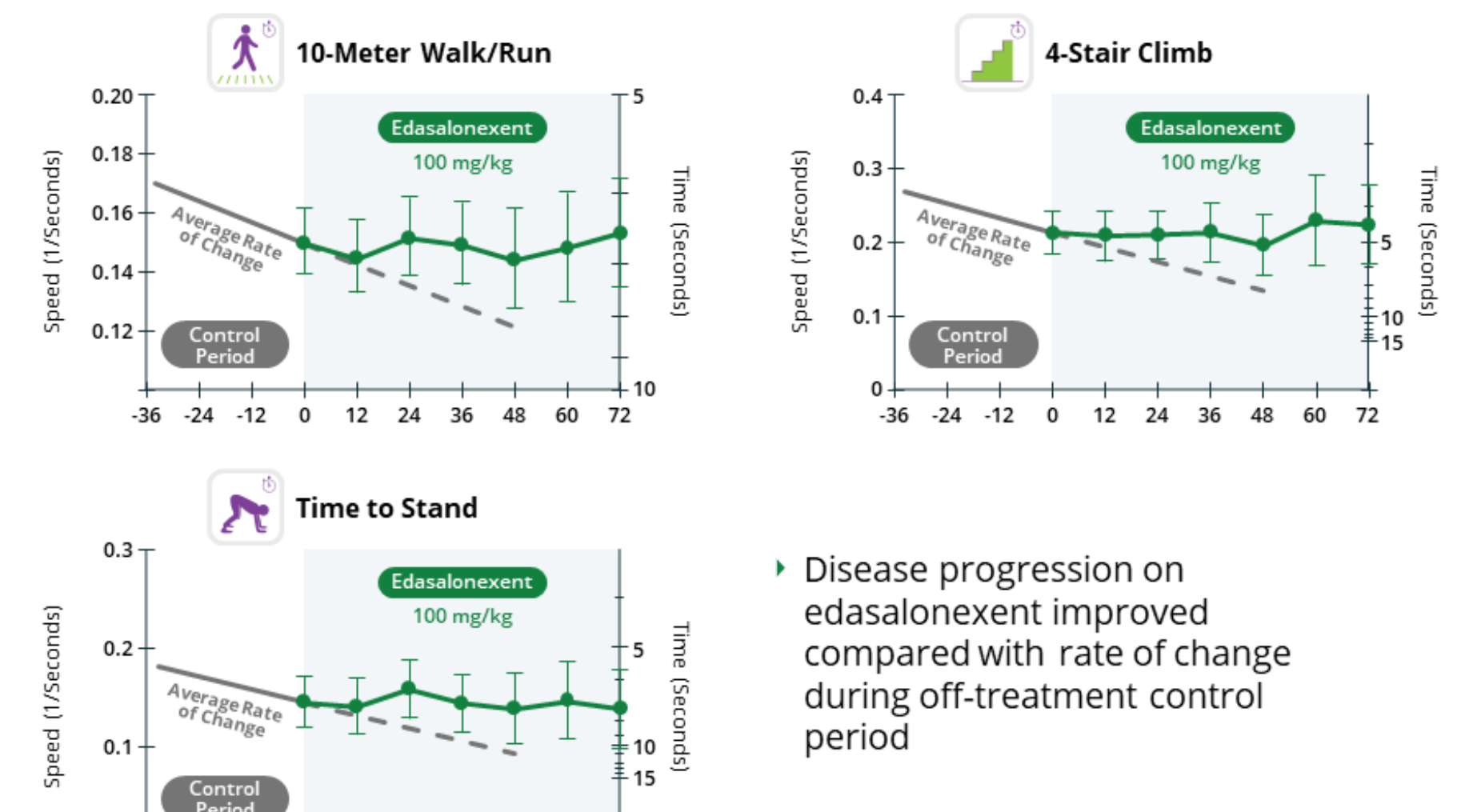
Edasalonexent Significantly Improved Rate of Change of Lower Leg Composite MRI T2

- On edasalonexent, the rate of change for the MRI T2 composite of the 5 lower leg muscles improved significantly compared to the rate of change during the off-treatment control period ($p < 0.05$ for 12, 24, 36 and 48 weeks)
- Stabilization of MRI T2 is consistent with slowing of disease progression also observed in function assessments



Means ± SEM shown; * $p < 0.05$ for repeated measure mixed model comparison with off-treatment period

Speed on All Timed Function Tests Stabilized with Edasalonexent Treatment



Disease progression on edasalonexent improved compared with rate of change during off-treatment control period

Means ± SEM shown. Includes data of all boys initially started on 100 mg/kg dose (n=16)

Conclusions

Conclusions: MRI T2 as Potential Marker of Clinical Outcome in Duchenne

- In the ImagingDMD database, the lower leg composite MRI T2 was highly correlated with timed function tests (TFTs) and 6-minute-walk distance, with correlations similar to previously reported values for the vastus lateralis and soleus FF.
- The lower leg composite MRI T2 correlated with current ability to complete TFTs, with 2 ms differences corresponding to clinically relevant functional changes.
- In MoveDMD, the off-treatment annualized rate of increase in the lower leg composite MRI T2 was 3.8 msec/year, and after 48 weeks of daily treatment with edasalonexent 100 mg/kg/day, the annualized rate was 0.3 msec/year ($p < 0.05$ compared with the off-treatment period).
- These results corroborate slowing of disease progression with functional measures and biomarkers observed with edasalonexent.
- Edasalonexent has disease-modifying potential in DMD, and a Phase 3 study is underway.

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